Journal of the American College of Cardiology
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Published by Elsevier, Inc.

Vol 55, No. 5, 2010
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2010.01.002

SCANNING THE LITERATURE

Summaries of Key Journal Articles

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Arrhythmias

Pulmonary Vein Isolation Combined With Substrate Modification for Persistent Atrial Fibrillation Treatment in Patients With Valvular Heart Diseases

Wang X, Liu X, Shi H, et al.
Heart 2009;95:1773–1783.

Study Question: Is radiofrequency catheter ablation (RFCA) of persistent atrial fibrillation (AF) safe and effective in patients with valvular heart disease (VHD)?

Methods: Circumferential pulmonary vein isolation and ablation of complex atrial electrograms were performed in 111 patients with persistent AF. Fifty-one patients had VHD (44 patients had a prosthetic mitral valve) and 60 patients did not have VHD. RFCA was performed with an irrigated-tip catheter and a ring catheter was used to map the pulmonary veins. Antiarrhythmic drug therapy was withdrawn at 3 months of follow-up and a 24-hour Holter monitor was performed at 2-month intervals. All patients were followed for 12 months.

Results: Freedom from AF/atrial tachycardia did not differ significantly between the patients with and without VHD (51% and 55%, respectively). After redo procedures, freedom from AF/atrial tachycardia also was similar in the patients with and without VHD (67% and 72%, respectively). Catheter entrapment in a prosthetic mitral valve occurred in one patient and was successfully managed by manual traction.

Conclusions: The efficacy and safety of RFCA of persistent AF are similar in patients with and without VHD.

Perspective: Entrapment of a ring catheter within a prosthetic valve can result in rapid hemodynamic decompensation. Although entrapment occurred in only one patient in this study, manual traction may not always be effective in freeing the catheter. Therefore, it would seem prudent to avoid introducing a ring catheter into the left atrium in patients with a prosthetic mitral valve undergoing RFCA of AF.

Summary written by: Fred Morady, MD

Cardiovascular Surgery

Endovascular Stent-Grafts for the Treatment of Abdominal Aortic Aneurysms: NICE Technology Appraisal Guidance

Hay N, McCracken F, Richardson J, George E, Barnett D.
Br 2009;95:1798–800.

Perspective: The top 10 points to remember about NICE guidance on the use of stent-grafts to treat abdominal aortic aneurysms (AAAs) are:

1: Endovascular aneurysm repair (EVAR) is recommended as a treatment option in patients with infrarenal AAAs for whom repair is considered appropriate.

2: Decisions as to whether to pursue EVAR or open AAA repair should be made jointly by the patient and clinician.

3: Aneurysm size and morphology, patient age, life

JACC, Vol 55, No. 5, 2010
February 2, 2010:507–14

expectancy and fitness, and long- and short-term benefits and risks of the procedures should figure into the decision about which route of AAA repair is appropriate.

4: EVAR should only be performed in centers of excellence by clinical teams experienced in management of patients with AAAs.

5: EVAR was not recommended for ruptured AAAs, except in the context of research.

6: EVAR has lower medium-term reduced rates of operative and aneurysm mortality.

7: EVAR, however, is not associated with a reduction in all-cause mortality long-term. EVAR is associated with increased complications and reinterventions compared with open repair.

8: As most reports comparing open repair and EVAR use older devices, the benefits of EVAR were likely greater than that seen in randomized control trials.

9: There was little or no difference in the initial procedure costs between EVAR and open repair.

10: In determining fitness for surgery, decisions over recommending EVAR versus open repair should be made on an individual basis, jointly between the patient and his/her clinician.

Summary written by: Gilbert Upchurch, Jr., MD

Mitral-Valve Repair for Mitral-Valve Prolapse

Verma S, Mesana TG.
N Engl J Med 2009;361:2261–2269.

Perspective: This summary describes a patient presenting with myxomatous degeneration of the mitral valve and severe mitral regurgitation (MR), and discusses the clinical problem, benefits, and risks of mitral valve repair. Ten points to remember are:

1: Mitral valve prolapse is the most common cause of MR in developed countries, with a prevalence of ~2.5%. In some patients, MR does not progress to severe, and life expectancy is normal; in other patients (~5-10%), MR progresses to severe, with adverse outcomes.

2: The mitral valve apparatus is comprised of mitral leaflets, annulus, chordae tendinae, papillary muscles, and left ventricular (LV) myocardium. The posterior mitral valve has three scallops. MR can be caused by malcoaptation of myxomatous, prolapsing leaflets, potentially exacerbated by mitral annular dilation.

3: When present, chronic severe MR leads to volume overload of the LV, with LV dilation, hypertrophy, neurohumeral activation, and heart failure. Elevation of left atrial pressure leads to left atrial enlargement, atrial fibrillation, pulmonary venous congestion, and pulmonary hypertension.

4: There are no randomized trials comparing medical therapy with surgery for MR caused by mitral valve prolapse. However, some studies suggest that survival is superior with early surgical intervention.

5: Mitral valve surgery can take the form of mitral valve replacement or repair. There are no randomized trials comparing mitral valve repair and replacement for MR caused by mitral valve prolapse. However, most observational studies suggest that outcomes are superior with mitral valve repair.

6: Surgical intervention generally is recommended for chronic severe MR and the presence of any symptoms, LV systolic dysfunction, significant LV enlargement, pulmonary arterial hypertension, or new atrial fibrillation. When surgery is indicated, current ACC/AHA and European Society of Cardiology (ESC) guidelines recommend preferential use of repair over replacement. If valve replacement is performed, subvalvular chordal attachments should be preserved.

7: There is debate regarding the use of 'prophylactic' mitral valve repair, used to treat chronic severe MR in an asymptomatic patient with none of the usual indications for surgery. ACC/AHA guidelines recommend prophylactic mitral valve repair if the likelihood of successful repair is >90%.

8: Mitral valve repair is a specialized technique that should be carried out by an experienced repair surgeon. Individual and institutional experience is crucial; and high volumes are associated with greater likelihood of valve repair rather than replacement, and lower procedural mortality.

9: Surgical valve repair can include resection of redundant or flail posterior segment(s); 'sliding plasty' to decrease posterior leaflet height; and chordal transposition, use of artificial chordae, and edge-to-edge repair for anterior leaflet pathology.

10: Adverse outcomes from surgery include death, required prolonged ventilatory support, renal insufficiency, stroke, thromboembolism, and late recurrence of MR.

Summary written by: David S. Bach, MD

General Cardiology

Effectiveness of Public Report Cards for Improving the Quality of Cardiac Care. The EFFECT Study: A Randomized Trial

Tu JV, Donovan LR, Lee DS, et al.
JAMA 2009;302:2330–2337.

Study Question: Does public reporting of cardiac quality indicators improve health care processes and patient outcomes?

Methods: The authors randomized 84 hospital corporations to early (January 2004) or delayed (September 2005) feedback of a public report card on their baseline performance (between April 1999 and March 2001) on a set of 12 process-of-care indicators for acute myocardial infarction (AMI) and 6 for congestive heart failure (CHF). Follow-up performance data (between April 2004 and March 2005) were collected.

Results: There was no difference in the composite AMI process-of-care indicator (absolute change, 1.5%) or the composite CHF process-of-care indicator (absolute change, 0.6%) between early versus late public report cards.

Conclusions: Public release of hospital-specific quality indicators did not significantly improve composite process-of-care indicators for AMI or CHF.

Perspective: This was a difficult randomized study to perform and the null results may have been partly due to improved performance of the control group (secondary to the Hawthorne effect). Public reporting can also have unintended consequences and carries significant cost. Although more open availability of outcome data is generally good, it has been hard to demonstrate whether the added cost of public reporting delivers any value to patients or physicians.

Summary written by: Hitinder S. Gurm, MBBS

Long-Term Results After Intracoronary Injection of Autologous Mononuclear Bone Marrow Cells in Acute Myocardial Infarction: The ASTAMI Randomised, Controlled Study

Beitnes JO, Hopp E, Lunde K, et al.
Heart 2009;95:1983–1989.

Study Question: What are the long-term clinical effects of intracoronary injection of autologous mononuclear bone marrow cell (mBMC) injection given in the setting of acute myocardial infarction (AMI)?

Methods: One hundred patients from the randomized, controlled ASTAMI study who underwent percutaneous coronary intervention in the setting of anterior wall ST-elevation myocardial infarction were re-assessed 3 years after inclusion. Outcome measures were change in left ventricular (LV) ejection fraction (primary), change in exercise capacity (peak VO_2) and quality of life (secondary), infarct size (additional aim), and safety.

Results: There were no significant differences between groups in change of global LV systolic function by echocardiography or magnetic resonance imaging (MRI) during follow-up. On exercise testing, the mBMC-treated patients had larger improvement in exercise time from 2-3 weeks to 3 years (1.5 minutes vs. 0.6 minutes, p = 0.05), but the change in peak oxygen consumption did not differ (3.0 ml/kg/min vs. 3.1 ml/kg/min, p = 0.75).

Conclusions: Intracoronary mBMC treatment in AMI is safe in the long-term. A small improvement in exercise time in the mBMC group was found, but no other effects of treatment could be identified 3 years after cell therapy.

Perspective: Previous studies of cell-based therapy for regeneration of infarcted myocardium had mixed results, with some trials reporting modest benefits. There does not appear to be a major safety issue with intracoronary mBMC in this study; however, the therapy appears largely ineffective. It may be time to hold off on additional similar human clinical trials until more effective forms of cell-based therapies demonstrate consistent, reproducible myocardial replacement in preclinical studies.

Summary written by: Daniel T. Eitzman, MD

Risk of Bleeding in Patients With Acute Myocardial Infarction Treated With Different Combinations of Aspirin, Clopidogrel, and Vitamin K Antagonists in Denmark: A Retrospective Analysis of Nationwide Registry Data

Sørensen R, Hansen ML, Abildstrom SZ, et al.
Lancet 2009;374:1967–1974.

Study Question: What is the long-term risk of bleeding among patients with myocardial infarction (MI) who are treated with aspirin, clopidogrel, or Coumadin, or any combination?

Methods: The authors used nationwide registries from Denmark to identify patients ages ≥30 years who had been admitted to the hospital with first-time MI between 2000 and 2005. Prescription claims starting at hospital discharge were used to determine the regimen prescribed according to the following groups: monotherapy with aspirin, clopidogrel, or vitamin K antagonist; dual therapy with aspirin plus clopidogrel, aspirin plus vitamin K antagonist, or clopidogrel plus vitamin K antagonist; or triple therapy including all three drugs. Risk of hospital admission for bleeding, recurrent MI, and death were assessed by Cox proportional hazards models with the drug exposure groups as time-varying covariates.

Results: During a mean follow-up of 476 days, 1,852 (4.5%) of 40,812 patients required hospitalization for a nonfatal

JACC, Vol 55, No. 5, 2010
February 2, 2010:507–14

bleeding event. The annual incidence of bleeding was 2.6% for the aspirin group, 4.6% for clopidogrel, 4.3% for vitamin K antagonist, 3.7% for aspirin plus clopidogrel, 5.1% for aspirin plus vitamin K antagonist, 12.3% for clopidogrel plus vitamin K antagonist, and 12.0% for triple therapy. Adjusted hazard ratios for bleeding were 1.33 for clopidogrel, 1.23 for vitamin K antagonist, 1.47 for aspirin plus clopidogrel, 1.84 for aspirin plus vitamin K antagonist, 3.52 for clopidogrel plus vitamin K antagonist, and 4.05 for triple therapy. Patients with nonfatal bleeding were at a higher risk of recurrent MI or death (37.9% vs. 18.4%) compared with patients without any bleeding events. Mean time from antithrombotic treatment to occurrence of a bleeding event varied from 169 days for clopidogrel monotherapy to 275 days for monotherapy with a vitamin K antagonist. Most nonfatal bleeding events were gastrointestinal.

Conclusions: Risk of hospital admission for bleeding increased with the number of antithrombotic drugs used in patients with MI.

Perspective: This study adds to evidence guiding physicians contemplating use of Coumadin in patients with a recent MI. Both triple and dual therapy with a vitamin K antagonist and clopidogrel was associated with extremely high risk of bleeding. Triple therapy or combination of Coumadin and clopidogrel should only be used after careful assessment of the risk–benefit ratio of the individual patient.

Summary written by: Hitinder S. Gurm, MBBS

Heart Failure/Transplant

The Yield of Risk Stratification for Sudden Cardiac Death in Hypertrophic Cardiomyopathy Myosin-Binding Protein C Gene Mutation Carriers: Focus on Predictive Screening

Christiaans I, Birnie E, van Langen IM, et al.
Eur Heart J 2009;Dec. 16:[Epub ahead of print].

Study Question: What is the value of risk stratification with genetic screening and clinical evaluations in patients with MYBPC3 gene mutations?

Methods: Two hundred and thirty-five mutation carriers were evaluated for the presence of hypertrophic cardiomyopathy (HCM) and risk factors. A clinical diagnosis of HCM was made in 53 carriers (22.6%).

Results: Disease penetrance was variable for all MYBPC3 gene mutations, and women were affected less often than men (15% and 32%, respectively; p = 0.003). One risk factor was present in 87 carriers and 9 had two or more risk factors. Twenty-five carriers (11%) with one or more risk factors and manifest HCM could be at risk for sudden cardiac death (SCD).

Conclusions: At first evaluation, one-quarter of asymptomatic carriers were diagnosed with HCM. Risk factors for SCD were frequently present, and 11% of carriers could be at risk for SCD. Predictive genetic testing in HCM families and frequent cardiac evaluation for presence of HCM and risk factors for SCD are justified until advanced age.

Perspective: Close clinical follow-up is indicated in relatives of patients with HCM. Knowledge of the mutation status may aid in follow-up if a likely causative mutation is identified. Most mutation carriers in the current study had the same Dutch founder mutation. However, because of the uncertainty of mutation causality in a diverse population and incomplete penetrance of mutation carriers, the added value of genetic testing remains unclear.

Summary written by: Daniel T. Eitzman, MD

Use of Genetics in the Clinical Evaluation of Cardiomyopathy

Judge DP.
JAMA 2009;302:2471–2476.

Perspective: The following are 10 points to remember about use of genetics in the clinical evaluation of cardiomyopathy:

1: Dilated cardiomyopathy (DCM) occurs in approximately 1 in 2,500 persons in the United States, and at least 20-35% of these patients have an affected family member. Every patient presenting with DCM should have a family history taken, including information about CM, sudden cardiac death, and syndromic features over at least three generations.

2: Since early treatment with angiotensin-converting enzyme (ACE) inhibitors has been shown to be beneficial in patients with left ventricular (LV) dysfunction, recognition of patients predisposed to DCM is clinically important.

3: Marked genetic heterogeneity complicates genetic testing for CM. Mutations in more than 35 genes have been associated with DCM, and genetic testing is clinically available for about half of these.

4: Mutations in the lamin A/C gene are found in 5-20% of patients with DCM, and may result in a worse prognosis. Ten percent of DCM patients have a mutation in a sarcomere gene.

5: Hypertrophic CM (HCM) occurs in about 1 in 500 persons in the United States, and is the most common cause of sudden

death in young athletes. Most mutations identified are found in sarcomere genes. Sarcomere mutations can thus cause either HCM or DCM.

6: Fabry disease is an X-linked lysosomal storage disease due to deficiency of α-galactosidase A that may lead to LV hypertrophy, which is difficult to distinguish from HCM due to other mutations. The Food and Drug Administration has approved recombinant enzyme treatment for this disease.

7: Familial amyloidosis may present with similar features to other forms of HCM, but with echocardiograms showing LV hypertrophy and electrocardiograms showing low voltage. Familial cardiac amyloid is often due to mutations in the transthyretin gene, and may be associated with neuropathy and chronic diarrhea.

8: The development of genomic DNA sequencing chips will reduce the cost and increase the feasibility of genetic testing to become more widely applied in clinical practice; however, translating the information into clinical practice will be a major hurdle.

9: Genetic testing may provide the diagnostic gold standard for screening of relatives, thus allowing for more vigilant follow-up of those with positive testing. However, decisions not to undergo screening are based on issues such as: a) concern about establishing a pre-existing condition, b) potential negative impact on future insurance premiums and employment, and c) uncertainty regarding mutation pathogenicity.

10: Genetic counseling should be provided prior to genetic testing.

Summary written by: Daniel T. Eitzman, MD

Interventional Cardiology

Contraindicated Medication Use in Dialysis Patients Undergoing Percutaneous Coronary Intervention

Tsai TT, Maddox TM, Roe MT, et al., on behalf of the National Cardiovascular Data Registry.
***JAMA* 2009;302:2458–2464.**

Study Question: What are the implications and prevalence of use of enoxaparin and eptifibatide in patients on dialysis who undergo percutaneous coronary intervention (PCI)?

Methods: The authors evaluated the outcome of 22,778 dialysis patients who underwent PCI between January 1, 2004, and August 31, 2008, at 829 hospitals. The main outcome measures were in-hospital bleeding and death.

Results: A contraindicated medication was used in 5,084 patients (22.3%). Of these, 2,375 (46.7%) received enoxaparin, 3,261 (64.1%) received eptifibatide, and 552 (10.9%) received both. Receipt of a contraindicated medication was associated with higher rates of in-hospital bleeding (5.6% vs. 2.9%) and death (6.5% vs. 3.9%). After multivariable adjustment, patients receiving contraindicated antithrombotics had significantly higher risks of in-hospital bleeding and death. In 10,158 patients matched by propensity scores, receipt of contraindicated antithrombotics remained significantly associated with in-hospital bleeding, but not in-hospital death. Among patients undergoing PCI with acute coronary syndrome, the use of enoxaparin versus unfractionated heparin, or eptifibatide versus abciximab was associated with an increased risk of in-hospital major bleeding.

Conclusions: Use of enoxaparin and eptifibatide in patients on dialysis was associated with a greater risk of bleeding.

Perspective: The fact that use of enoxaparin and eptifibatide increases risk of bleeding in patients on dialysis is not a surprise. I was, however, surprised by how commonly these drugs are used in this population. Alternatives (unfractionated heparin, bivalirudin, abciximab) that are safer in patients on dialysis should be used to reduce the bleeding risk in this population.

Summary written by: Hitinder S. Gurm, MBBS

Noninvasive Cardiology

Projected Cancer Risks From Computed Tomographic Scans Performed in the United States in 2007

de Gonzalez AB, Mahesh M, Kim K, et al.
***Arch Intern Med* 2009;169:2071–2077.**

Study Question: What is the future cancer risk from current computed tomographic (CT) scan use in the United States?

Methods: The authors estimated the frequency of different types of CT scans performed using Medicare claims data and the IMV Medical Information Division survey of CT scan use in 2,451 US facilities in 2007. The age and sex distribution for each CT scan type was estimated using a large national commercial insurance database. These estimates were projected to the age-sex distribution of the US population. Patients dying within 5 years of CT scan were excluded.

JACC, Vol 55, No. 5, 2010
February 2, 2010:507–14

Results: The authors estimated that CT scans performed in 2007 may result in 29,000 (95% UL 15000-45000) excessive malignancies. The largest risk was from scans of the abdomen and pelvis (n = 14,000) (95% UL, 6,900-25,000), followed by chest (n = 4,100) (95% UL, 1,900-8,100), and head (n = 4,000) (95% UL, 1,100-8,700), and chest CT angiography (n = 2,700) (95% UL, 1,300-5,000). Lung cancer was the most common projected radiation-related cancer (n = 6,200) (95% UL, 2,300-13,000) followed by colon cancer (n = 3,500) and leukemia (n = 2,800). Approximately a third of the projected cancers were due to scans performed between the ages of 35 to 54 years compared with 15% of those <18 years. The projected malignancies were expected to be more common in females (66%).

Conclusions: Current CT scan use is expected to contribute to a large number of future malignancies.

Perspective: This study adds to the growing awareness of radiation risks associated with medical procedures, which has resulted in lower use of radiation-based imaging in the pediatric population; however, more needs to be done to lower radiation use in young and middle-aged adults. Dedicated quality improvement initiatives have been successful at reducing radiation dose with CT angiography, and similar efforts are needed to minimize the risk with all types of CT scans.

Summary written by: Hitinder S. Gurm, MBBS

Prevention/Vascular

Physical Exercise Prevents Cellular Senescence in Circulating Leukocytes and in the Vessel Wall

Werner C, Fürster T, Widmann T, et al.
Circulation 2009;120:2438–2447.

Study Question: What are the effects of exercising on vascular telomere biology and endothelial apoptosis in mice, and what are the effects of long-term endurance training on telomere biology in humans?

Methods: C57/Bl6 mice were randomized to voluntary running or no running wheel conditions for 3 weeks. Exercise telomerase activity was evaluated in the thoracic aorta and in circulating mononuclear cells and compared with sedentary controls. Telomere biology in circulating leukocytes of young and middle-aged track and field athletes was analyzed and compared to untrained individuals.

Results: Exercise upregulated telomerase activity in the thoracic aorta and in circulating mononuclear cells compared with sedentary controls. Mice preconditioned by running exhibited a marked reduction in lipopolysaccharide-induced aortic endothelial apoptosis. Transgenic mouse studies showed endothelial stress resistance after physical activity. Peripheral blood leukocytes isolated from endurance athletes showed increased telomerase activity, expression of telomere-stabilizing proteins, and downregulation of cell-cycle inhibitors compared with untrained individuals. Long-term endurance training was associated with reduced leukocyte telomere erosion compared with untrained controls.

Conclusions: Physical activity regulates telomere-stabilizing proteins in mice and in humans and thereby protects from stress-induced vascular apoptosis.

Perspective: Regular exercise training and better fitness are associated with many positive effects including blood pressure control, insulin sensitivity, less abdominal fat, better lipid profile, reduction in systemic inflammatory markers, and improved stress response. This study provides evidence for one of many potential molecular explanations for decreasing cardiovascular and overall mortality in fit men and women.

Summary written by: Melvyn Rubenfire, MD

Effects of Liraglutide in the Treatment of Obesity: A Randomised, Double-Blind, Placebo-Controlled Study

Astrup A, Rössner S, Van Gaal L, et al., on behalf of the NN8022-1807 Study Group.
Lancet 2009;374:1606–1616.

Study Question: What is the effect of liraglutide, a glucagon-like peptide-1, on bodyweight and tolerability in obese individuals without type 2 diabetes?

Methods: A double-blind, placebo-controlled 20-week trial, with open-label orlistat comparator was conducted in 19 sites in Europe. A total of 564 individuals (18-65 years of age, body mass index 30-40 kg/m^2) were randomly assigned, with a telephone or web-based system, to one of four liraglutide doses (1.2 mg, 1.8 mg, 2.4 mg, or 3.0 mg, n = 90-95) or to placebo (n = 98) administered once a day subcutaneously, or orlistat (120 mg, n = 95) three times a day orally. All individuals had a 500 kcal per day energy-deficit diet and increased their physical activity throughout the trial. An 84-week open-label extension followed.

Results: Mean weight loss with liraglutide 1.2-3.0 mg was 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg compared with 2.8 kg with placebo and 4.1 kg with orlistat, and was 2.1-4.4 kg greater than that with placebo. More individuals (76%) lost more than 5% weight with liraglutide 3.0 mg than with placebo (30%) or orlistat (44%) ($p < 0.0001$ for each). Liraglutide reduced blood pressure at all doses, and reduced the prevalence of prediabetes (84-96% reduction) with 1.8-3.0 mg per day.

Conclusions: Liraglutide treatment over 20 weeks is well toler-

ated, induces weight loss, improves certain obesity-related risk factors, and reduces prediabetes.

Perspective: The GLP-1 class of drugs, including FDA approved exenatide (Byetta®, Amlyin Pharmaceuticals), is associated with a dose-dependent weight loss, improved glycemic control and β-cell function, and lowers systolic blood pressure. GLP-1 suppresses appetite and energy intake. Long-term studies will be necessary to determine the cost-effectiveness of this relatively expensive strategy compared to metformin and other weight loss options.

Summary written by: Melvyn Rubenfire, MD

10-Year Follow-up of Diabetes Incidence and Weight Loss in the Diabetes Prevention Program Outcomes Study

Diabetes Prevention Program Research Group.
***Lancet* 2009;374:1677–1686.**

Study Question: What is the persistence of benefit seen from metformin and intensive lifestyle intervention in preventing diabetes in high-risk patients enrolled in the Diabetes Prevention Program (DPP) randomized clinical trial?

Methods: All participants in the three original DPP patient groups (lifestyle intervention, metformin, placebo) were offered lifestyle intervention in this follow-up study, due to the demonstrated efficacy. The metformin group subjects continued therapy. Primary endpoint was development of diabetes, according to American Diabetes Association criteria. Analysis was by intention to treat.

Results: Among 3,150 original enrollees, 2,166 (88%) enrolled for a median additional follow-up of 5.7 years, for a median total follow-up of 10.0 years. The original lifestyle group lost, then partly regained weight, and the metformin group maintained modest weight loss. Incidence rates of diabetes during the original study were 4.8 cases per 100 person-years in the lifestyle intervention group, 7.8 in the metformin group, and 11.0 in the placebo group. Incidence rates were similar, at 5.9 per 100 person-years for lifestyle, 4.9 for metformin, and 5.6 for placebo. Diabetes incidence in the 10 years since DPP randomization was reduced by 34% in the lifestyle group and 18% in the metformin group compared with placebo.

Conclusions: During extended follow-up, incidence rates for diabetes in the former metformin and placebo groups decreased to equal those in the former lifestyle group, although the cumulative incidence of diabetes remained lowest in the lifestyle group. Prevention or delay of diabetes with lifestyle intervention or metformin can persist for at least 10 years.

Perspective: The DPP study was an emphatic demonstration of the profound impact lifestyle intervention can have on development of diabetes. Important take-home points from this and the initial study are: Lifestyle intervention (and metformin) is highly effective in achieving weight loss and preventing the development of diabetes in an at-risk population. Blood pressure and lipid profiles improved with the weight loss. More important will be an evaluation of the cost-effectiveness of this lifestyle intervention, and the applicability in real-life clinics.

Summary written by: James B. Froehlich, MD

Major Bleeding, Mortality, and Efficacy of Fondaparinux in Venous Thromboembolism Prevention Trials

Eikelboom JW, Quinlan DJ, O'Donnell M.
***Circulation* 2009;120:2006–2011.**

Study Question: What is the association between major bleeding and mortality as well as efficacy of fondaparinux versus low molecular weight heparin (LMWH) or placebo for the prevention of venous thromboembolism (VTE)?

Methods: The authors analyzed data combined from all randomized, controlled trials of fondaparinux 2.5 mg daily versus LMWH or placebo for the prevention of VTE during hip fracture surgery, hip replacement surgery, major knee surgery, elective abdominal surgery, or high-risk acutely ill medical patients, in eight separate studies. They used Cox proportional hazards modeling to study the association between major bleeding and death at 30 days.

Results: Subjects developing major bleeding were older, more likely male, had lower body weight and lower creatinine clearance, and were more likely to receive fondaparinux. Mortality risk was higher among subjects with major bleeding (8.6% vs. 1.7%). Mortality was lower among subjects treated with fondaparinux in the presence of major bleeding (6.8% vs. 11.4%) or without major bleeding (1.5% vs. 1.9%; p value for heterogeneity = 0.47).

Conclusions: Major bleeding in hospitalized surgical and medical patients participating in VTE prevention trials is a strong predictor of mortality.

Perspective: It is not surprising that major bleeding was associated with increased mortality; but importantly, fondaparinux was associated with improved mortality regardless of the presence of major bleeding. One can also conclude that the benefit from thromboprophylaxis with fondaparinux outweighs any increased risk of bleeding; thus, concern for bleeding risk in the setting of VTE prophylaxis is misguided, and underestimates the benefit.

Summary written by: James B. Froehlich, MD

JACC, Vol 55, No. 5, 2010
February 2, 2010:507–14

C-Reactive Protein Concentration and Risk of Coronary Heart Disease, Stroke, and Mortality: An Individual Participant Meta-Analysis

The Emerging Risk Factors Collaboration.
Lancet 2009;Dec 22:[Epub ahead of print].

Study Question: What is the association of C-reactive protein (CRP) concentration and risk of vascular and nonvascular outcomes, and is the relationship causal?

Methods: A collaborative study using meta-analysis was conducted between investigators of 54 prospective studies of cardiovascular risk factors who provided data regarding CRP and outcomes. The cohort included 160,309 people without a history of vascular disease (i.e., 1.31 million person-years at risk, 27,769 fatal or nonfatal disease outcomes). Within-study regression analyses were adjusted for within-person variation in risk factor levels. The primary outcome was coronary heart disease (CHD), with subsidiary analyses of stroke by subtype, death from vascular disease, and aggregate of nonvascular death.

Results: Log_e CRP concentration was linearly associated with several conventional risk factors and inflammatory markers, and nearly log-linearly with the risk of ischemic vascular disease and nonvascular mortality. Significant increases in risk ratios (RRs) were found for CHD per 1-standard deviation higher log_e CRP concentration (threefold higher) RR 1.63 when initially adjusted for age and sex only, and RR 1.37 when adjusted further for conventional risk factors; 1.44 and 1.27 for ischemic stroke; 1.71 and 1.55 for vascular mortality; and 1.55 and 1.54 for nonvascular mortality. After adjustment for fibrinogen, corresponding RRs were 1.23 for CHD; 1.32 for ischemic stroke; 1.34 for vascular mortality; and 1.34 for nonvascular mortality.

Conclusions: CRP concentration has continuous associations with risk of CHD, ischemic stroke, vascular mortality, and death from several cancers and lung disease that are each of broadly similar size. Associations with ischemic vascular disease depend considerably on conventional risk factors and other markers of inflammation.

Perspective: There is debate about the clinical utility of CRP for risk assessment in cardiovascular disease as well as whether it is a causal relationship or simply a biomarker of risk. This study adds to the abundant literature supporting CRP as a risk marker for cardiovascular events and mortality. This study showing attenuation of attributable risk when corrected for fibrinogen, and recent studies showing no relationship between genetic polymorphisms associated with higher CRP and cardiovascular disease imply that CRP is a risk marker, but not a risk factor for cardiovascular events.

Summary written by: Melvyn Rubenfire, MD

Association of Circulating Cholesteryl Ester Transfer Protein Activity With Incidence of Cardiovascular Disease in the Community

Vasan RS, Pencina MJ, Robins SJ, et al.
Circulation 2009;120:2414–2420.

Study Question: What is the relationship between plasma cholesteryl ester transfer protein (CETP) activity and the incidence of cardiovascular disease (CVD)?

Methods: Plasma CETP activity was measured in 1978 Framingham Heart Study participants (mean age, 51 years; 54% women) who attended a routine examination from 1987 to 1990 and were free of CVD. On follow-up (mean, 15.1 years), 320 participants experienced a first CVD event (fatal or nonfatal coronary heart disease, cerebrovascular disease, peripheral vascular disease, or heart failure).

Results: In adjusted multivariable analyses, plasma CETP activity was related inversely to the incidence of CVD events (hazard ratio [HR] for activity, at or above the median of 0.72; 95% confidence interval, 0.57-0.90; p = 0.004 [compared with below median]; HR per standard deviation increment, 0.86; 95% confidence interval, 0.76-0.97; p = 0.01). The inverse association of CETP activity with CVD incidence remained robust in time-dependent models updating standard risk factors every 4 years, and was maintained in analyses of incident "hard" CVD events (myocardial infarction, stroke, or heart failure).

Conclusions: Lower plasma CETP activity was associated with greater CVD risk. These observations, if confirmed, challenge the concept that CETP inhibition may lower CVD risk.

Perspective: Although HDL levels are inversely related to the risk of CVD, pharmacologic strategies designed to raise HDL based on CETP inhibition have not produced beneficial vascular effects, and may even be harmful. Studies addressing relationships between genetic CETP abnormalities and circulating CETP concentrations with CVD have been controversial. The current study adds important prospective data to this controversial area and suggests CETP inhibitors will not have beneficial effects on CVD events, and may lead to harm.

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